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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/748,475 | 12/30/2003 | Masad J. Damha | MGU-0025 | 7556 |

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| ART UNIT | PAPER NUMBER |
| 1635 | |

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/748,475 | DAMHA ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly Chong | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/11/2006 has been entered.

### Status of the Application

Claims 1 and 3-8 are pending and currently under examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "...a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The claims are drawn to a broad genus of compositions comprising an inhibitory agent comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1and wherein the inhibitory agent binds to the RNase H domain of retroid reverse transcriptase thereby inhibiting RNase H activity.

The instant claims and specification fail to provide adequate written description of the genera of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that is commensurate in scope with the breadth of the instant invention:

binding of the inhibitory agent to any RNase H domain of retroid reverse transcriptase thereby inhibiting any RNase H activity.

The specification, in Example 8, discloses an embodiment wherein HIV-1 reverse transcriptase RNase H is inhibited using RNA dumbbells. The specification, in Example 11, discloses a specific embodiment wherein RNA dumbbells were used to inhibit either *E. coli* or Human RNase H activities. The specification, in Example 12, discloses a specific embodiment wherein RNA dumbbells and RNase Hare crosslinked.

The specification does not provide a core structure sequence of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that would bind to bind to any RNase H domain of retroid reverse transcriptase and inhibit the activity of any RNase H. Therefore in only disclosing minimal examples of RNA dumbbells that inhibit RNase H activity in an assay, the specification does not provide adequate written description for the genus of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that provide the asserted function of binding to any RNAse H domain and inhibition RNase H activity.

The specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention. Furthermore, the state of the art cannot provide the specific guidance as evidenced by Joshi et al. (Journal of Virology 2002).

Joshi et al. teach identification of inhibitory agents targeted to the reverse transcriptase of HIV-1 is accomplished by screening a library of randomized sequences to find an inhibitory agent capable of binding to the reverse transcriptase region with high affinity. Joshi et al. further teach the sequences identified as binding with high affinity lack primary sequence homology to each other (see page 6545). Because the prior art teach identification of inhibitory agents that bind with high affinity to the reverse transcriptase region of HIV-1 must be done by screening a library of randomized sequences and teach each of the identified sequences lack homology with each other, one of skill in the art would not know which sequence, from a broad genus of inhibitory agents claimed, would provide the instantly claimed function of binding to any reverse transcriptase and inhibiting the function of any RNase H.

Moreover, MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274; 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further

comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that would bind to the RNase H domain and inhibit RNase H activity.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

***Response to Applicant's Arguments***

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wasner et al. (Document AM on Form PTO-1449 filed 10/04/2004) in view of Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) and in further view of Ray et al. (FASEB J. 2000) is maintained.

Applicant's arguments filed 07/11/2006 are acknowledged but are not found persuasive. Applicant argues the claimed inhibitory agent is a nucleic acid based ligand and not an antisense or a synthetic ribozyme. Applicants further argue that Hannoush et al. teach the use of hairpins in the design of ribozymes as well as antisense agents and further Ray et al. teach the use of PNAs for the strong DNA affinity in antisense molecules and therefore there would be no suggestion or motivation to combine these teachings with that of Wasner et al. "...to produce, with a reasonable expectation of success, an inhibitory agent which binds to the RNase H domain of a retroid virus reverse transcriptase thereby inhibiting the RNase H activity...".

As stated in the Office action filed 01/11/2006 and the After final filed 06/12/2006 and further reiterated herein, Wasner et al. teach a nucleic acid compound for inhibiting the RNAse H activity of a retroid virus reverse transcriptase comprising two complementary strands 18-23 nucleotides in length, wherein the strands can be RNA or DNA or both and further wherein the duplex comprise 3', 5'-linked or 2', 5'-linked RNA (see Figure 1 and Table 1). Wasner et al. recognized that although the nucleic acid duplexes were capable of inhibiting RNase H activity, they had low thermal stability properties (see page 7482 and Table 2). Therefore, one of skill in the art would have been motivated to incorporate the tetranucleotide loops identical to SEQ ID NO. 1 taught by Hannoush et al. because Hannoush et al. teach hairpin structures comprising tetranucleotide loops are extremely stable and are important structural motifs for the design of nucleic acid aptamers. Moreover, Wasner et al. specifically teach along with the utility of said nucleic acid molecules and their analogues in antiretroviral applications, "...hairpin 'aptamers' designed with the proper combination 2', 5 RNA and (complementary) RNA segments may inhibit the removal of the RNA component of the RNA:DNA hybrid formed during reverse transcription." Therefore, one of skill in the art would have clearly been motivated to incorporate hairpin structures into the inhibitory agent taught by Wasner et al. for the use in inhibition RNase H activity. Ray et al. teach peptide nucleic acids are synthetic molecules that can bind with high sequence specificity to a chosen target in a gene sequence and further Ray et al. teach that hybrid nucleic acid complexes containing a peptide nucleic acid exhibit extreme thermal

stability and unique ionic strength. Therefore, one of skill in the art would have been motivated to incorporate PNAs to increase duplex stability in a duplex nucleic acid.

The teaching of Wasner et al:, Hannoush et al. and Ray et al. provide a reasonable expectation of success given that Wasner et al. and Hannoush et al. teach inhibition of RNAse activity using said duplex and because Ray et al. teach targeting a gene sequence using a duplex comprising a peptide nucleic acid and further teach inhibition of gene activity using a duplex comprising a peptide nucleic acid. Additionally, one would have a reasonable expectation of success given that Hannoush et al. teach that an oligonucleotide duplex comprising a tetranucleotide loop having the sequence identical to SEQ ID NO. 1 increase the duplex thermostability and further teach the actual hybrid duplex taught in Wasner et al., which was shown to inhibit RNase H activity, is more stable when linked to the said tetranucleotide loop.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The rejection of record of claims 1, 3-8 under 35 U.S.C. 103(a) as being unpatentable over Hannoush et al. (Document AE on Form PTO-1449 filed 10/04/2004) in view of Denisov et al. (Nucleic Acids Research, 2001) is withdrawn in response to Applicant's claim amendments.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635